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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,569	01/16/2001	Roger J. Davis	10363-003004 / UMMC Ref.:	9227

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/761,569	DAVIS ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/30/04.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _____ is/are pending in the application. ~~65-75~~ 51-76

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 51-64, 66-74

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected. 65, 75-76

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 7/30/04, has been entered.
Claim 65 has been amended.
Claims 75-76 have been added.

Applicant's election without traverse of Group I (claim 65) drawn to a method treating an MKK-mediated disorder in a patient with an antibody that binds MKK3 (SEQ ID NO: 2) has been acknowledged.

Claims 65 and newly added 75-76 are being acted upon as the elected invention.

Claims 1-50 have been canceled previously.

Claims 51-64 and 66-74 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed in applicant's amendment, filed 7/30/04.
The rejections of record can be found in the previous Office Action, mailed 1/29/04.

3. Claim 65 and newly added 75-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant's arguments, filed 7/30/04, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant asserts that neither Bokemeyer nor Wolf of record discuss the role of MKKs in disease states in any particular details and whether inhibitors of MKKs would be useful for treating certain diseases, particularly the role of MKK3 in rheumatoid arthritis.

Rather applicant asserts that the instant claims are enabled by the teachings provided in the specification (e.g. pages 6, 10, 16-17, 26 and 46-48, including Examples 5-6) and by the knowledge of those skilled in the art (e.g. Raingeaud et al., J. Biol. Chem. 270: 7420-7426, 1995), Chabaud-Riou et al., Am. J. Pathol. 164: 177-184, 2004). Applicant asserts that any skilled practitioner would have appreciated that an inhibitor of MKK3 activity could be used to reduce expression of inflammatory cytokines and inflammatory disorder in general.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

The following of record is reiterated for applicant's convenience.

The specification describes assays for determining whether a given compound possess certain desired characteristics and identifies some broad categories of compounds that might work, these description without more precise guidelines amount to little more that a starting point, a direction for further research . The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the various in vitro assays disclosed in the application as filed accurately reflects the relative ability of antibodies that bind MKK3 to inhibit rheumatoid arthritis encompassed by the claimed therapeutic strategies (e.g. see page 10, paragraphs 1-3 of the instant specification).

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively treat any disorder or reach any therapeutic endpoint in humans by administering antibodies that bind MKK3. The specification does not teach how to extrapolate data obtained from in vitro assays determining kinase expression and activity to the development of effective in vivo human therapeutic methods to inhibit rheumatoid arthritis. Therefore, it is not clear that the skilled artisan could predict the efficacy of antibodies that bind MKK3, in turn, would treat the variety of disorders and conditions, including rheumatoid arthritis.

Further, it is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus/insult occur at the same or nearly the same time. Immunosuppression is much easier to achieve under such controlled conditions that experienced in the human immunoregulatory diseases such as autoimmunity targeted by the claimed invention. With respect to in vivo studies, animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission.

The following is noted in determining the role of kinases, such as the MAP kinases, in signal transduction pathways and various pathophysiologic processes.

For example, Bokemeyer et al. (J Am Soc Nephrol 13: 1473-1480, 2002) reports that "Although an extensive body of data describes the pivotal role of ERK signaling pathway in the control of cellular proliferation in vitro, little is know regarding the roles of ERK1 and ERK2 in physiologic or pathophysiologic conditions or their activation in vivo" (page 1473, paragraph 1 of the Introduction). Furthermore, it is noted here that "the physiologic function of most of the growing group of MAP kinases, including stress-activated protein kinases even in vitro is less well defined". To indicate the importance for some objective evidence in determining the ability to inhibit a kinase in disorders, the Discussion discloses that "although our data suggested that ERK contributed to glomerular proliferation in vivo, no interventional studies were available that examined whether inhibition of ERK activation could prevent cellular proliferation in inflammatory diseases, especially with respect to the kidney" (page 1478, column 1). Bokemeyer et al. also concludes that "it is essential to establish the pathophysiologic relevance of the MEK-ERK module in each form of immune injury, to identify the diseases that are most likely to benefit from treatment with a MEK inhibitor" (see page 1479, column 2, paragraph 1 in the Discussion). "Such studies, other than this study, have not bee performed".

Wolf et al. (Israel Medical Association Journal 4: 641-647, 2002) address the ERK cascade in the pathogenesis of human diseases (see entire document, including page 644, column 2). For example, "laboratories have been trying to elucidate the role of the MAP kinase cascades and the ERK cascade in particular. Although the detection of ERK activation is fairly simple, interpretation of these studies mandates caution. One should bear in mind that the ERK cascade participates in various ways in many physiologic processes, thus making it hard to discern its exact role in disease states". Wolf et al. concludes that stating that: "Despite these encouraging developments, one must remember that since the activation of ERKs occur in so many physiologic processes, which obviously must not be inhibited, its inhibition in a non-specific manner might be harmful and thus prevent the clinical use of ERK cascade inhibitors" (see page 646, column 1, paragraph 2).

There appears to be insufficient evidence that applicant's reliance on the characterization of MKK3 would indicate that the claimed therapeutic modalities based upon anti-MMK3 antibody antagonists would be effective on either acute or chronic diseases, commensurate in scope with the claimed invention. Although a kinase may be involved in cell signaling pathways in normal and pathologic conditions, the ability of an antibody to such a kinase to lead some effective therapeutic endpoint will depend on the kinase, the antagonist and the particular nature of the disease (e.g. acute versus chronic). In humans, the claimed diseases encompassed by the claimed methods are already established before therapy is offered. There are distinct differences in the kinase requirements for particular types of inflammation.

There is insufficient objective evidence that the binding of a single compound such as an anti-MMK3 antibody to a kinase can be extrapolated to predict the efficacy of this anti-MMK3 antibody can inhibit or treat rheumatoid arthritis.

The reliance by applicant on Raingeaud et al. (J. Biol. Chem. 270: 7420-7426, 1995) and Chabaud-Riou et al. (Am. J. Pathol. 164: 177-184, 2004) does not provide for the nexus or extrapolation of treating rheumatoid arthritis with anti-MKK antibodies. While these references indicated MKKs are important regulators in signaling in cells, including synoviocytes, these references do not provide for the ability of anti-MKK antibodies to act as an inhibitor of such signaling, particularly the ability of anti-MKK antibodies to inhibit MKK-mediated responses in vivo, including a chronic disease such as rheumatoid arthritis.

Given the relative incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims, a rejection under 35 USC 112, first paragraph for lack of enablement is appropriate. Also see MPEP 2164.08

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies for antibodies that inhibit kinases and, in turn, inhibit inflammatory conditions, including rheumatoid arthritis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting rheumatoid arthritis encompassed by the claimed invention.

Applicant's arguments have not been found persusasive.

4. Applicant's amended claims, filed 7/30/04, have obviated the previous rejections under 35 U.S.C. § 112, second paragraph, with respect to the recitation of "MKK-mediated disorder" and "modulates MKK activity" as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. No claim is allowed.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
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October 18, 2004